A Phase II Study of Induction Therapy with Carboplatin and Gemcitabine among Patients with Locally Advanced Non-small Cell Lung Cancer

J.G.J.V. Aerts, MD, PhD,† V. Surmont, MD,* R.J. van Klaveren, MD, PhD,* K.Y. Tan, MD,† S. Senan, MD, PhD,‡ G. van Wijhe,* R. Vernhout,* G.T, Verhoeven, MD, PhD,|| H.C. Hoogsteden, MD, PhD,* and J.P. van Meerbeeck, MD, PhD§*

Introduction: The objectives of this trial were to evaluate the activity and safety of gemcitabine carboplatin as induction therapy in patients with locally advanced non-small cell lung cancer

Methods: Patients received two cycles of gemcitabine (1250 mg/m^2 on day 1 and 8), plus carboplatin (area under the curve = 5 on day 1), after which response was established. Patients received a third course only in the case of an objective response (OR). Non-responding patients were directly irradiated. Toxicity was assessed according to the NCI-CTC version 2, radiation toxicity was assessed according to RTOG criteria. Response evaluation was performed according to RECIST criteria.

Results: We identified 42 patients, of whom 37 were eligible. Of these, 51% (95% CI, 34%-68%) achieved an OR, all partial responses. No disease progression on therapy was established. Toxicity was mostly hematological: 35% trombocytopenia grade 3 and 4, and 40% neutropenia grade 3 and 4. No severe bleeding or hospitalization because of febrile neutropenia occurred.

Conclusions: Gemcitabine and carboplatin administered according to a 3-week schedule is an active and safe induction regimen. Pending the results of a phase III study, we believe that it is a reasonable alternative among patients for whom cisplatin-based chemotherapy is contraindicated.

Key Words: Locally advanced NSCLC, Gemcitabine, Carboplatin, Induction.

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The combination of platinum-based chemotherapy and thoracic irradiation is considered standard therapy in patients with unresectable locally advanced non-small cell lung cancer (NSCLC). In a number of randomized studies and a meta-analysis, chemotherapy added to radiotherapy improved survival compared with radiotherapy alone.[1]

Recent studies claim concurrent chemo-irradiation to be superior to sequential therapy as it achieves higher response rates and adds 7% on long-term survival benefit.[2,3] However, the optimal chemo- and radiotherapy combination is yet unknown, and its major drawback is its increase in toxicity, both hematologic and non-hematologic (mucositis, pneumonitis, and esophagitis). This is the reason that a recent meta-analysis and the NICE guideline restrict the use of concurrent chemo-radiotherapy to selected patients.[2] Although sequential therapy is not the standard of care in the United States, it is still widely used in Europe, mainly because of logistical reasons.

In the sequential treatment setting, response to induction chemotherapy is an important variable in qualifying for subsequent radiotherapy.[1,4] A doublet of platinum combined with a third-generation chemotherapeutic agent is considered to be the most active induction regimen. One of these third-generation agents is gemcitabine. In a recent meta-analysis, gemcitabine-containing regimens led to a better survival than other third-generation drug combinations in patients with advanced NSCLC.[5]

Because of its more favorable toxicity profile, carboplatin is often preferred to cisplatin.[6,7] The most frequently used regimen in the United States combines carboplatin and paclitaxel. In a recent meta-analysis, it was concluded that cisplatin combinations have a survival benefit compared with carboplatin combinations in advanced NSCLC,[7] but in phase III studies in which gemcitabine-cisplatin and gemcitabine-carboplatin were compared, no survival benefit for the cisplatin combination could be demonstrated in advanced disease.[6,8]

The aim of the present study was to investigate the activity and toxicity of the combination of carboplatin and gemcitabine as an induction regimen for stage III NSCLC.

PATIENTS AND METHODS

The study was conducted in three Dutch hospitals in Rotterdam (Erasmus MC, Sint Franciscus Gasthuis, and

*Department of Pulmonary Diseases, Erasmus MC, Rotterdam; †Department of Pulmonary Diseases, Sint Franciscus Gasthuis, Rotterdam; ‡Department of Radiotherapy, Free University Amsterdam, Amsterdam; ||Dept. of Pulmonary Diseases, MCRZ Rotterdam, The Netherlands; §Department of Pulmonary Diseases, University Hospital, Ghent, Belgium
Address for correspondence: J.G.J.V. Aerts, M.D. Ph.D., Department of Pulmonary Diseases, Sint Franciscus Gasthuis, Kleiweg 500, 3045PM Rotterdam. E-mail: j.aerts@sfg.nl

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MCRZ) and was approved by the local ethical committees of each participating center.

Eligible chemonaive patients had to have a histological or cytological diagnosis of locally advanced NSCLC. In the case of presumed stage IIIA disease, tissue confirmation of N2 involvement was required. In the case of stage IIIB disease, patients with N3 (excluding supraclavicular lymphnodes) or T4 (excluding pleural fluid) were eligible. Other criteria were: measurable disease according to RECIST criteria, age older than 18 years, World Health Organization performance status 2 or less, adequate bone marrow reserve (hemoglobin >10 mg/dL or 6 mmol/L, white blood cell count higher then 4.0×10^9/L, absolute neutrophil count $>2.0 \times 10^9$/L, platelet count $>100 \times 10^9$/L), and a calculated creatinine clearance of at least 60 mL/min. Women of childbearing age were asked to use adequate contraceptive methods.

Exclusion criteria were the presence of other malignancies (previous or current), except adequately treated in situ carcinoma of the uterine cervix or basal or squamous cell carcinoma of the skin, or a previous malignancy more than 5 years ago without evidence of recurrence; pregnancy and/or breast feeding; use of any investigational agent in the month before enrolment into the study; uncontrolled infections and signs or symptoms of metastases; a weight loss of more than 10% in the preceding 3 months.

Pretreatment evaluation included a complete medical history and physical examination, chest radiograph and computed tomographic scanning of thorax and upper abdomen, pulmonary function testing with diffusion capacity, routine blood sampling, urine analysis, and electrocardiogram. All patients had to give written informed consent.

Treatment:

The treatment scheme is presented in Figure 1. Chemotherapy consisted of two courses of gemcitabine and carboplatin as a 21-day regimen. Gemcitabine was given at a dosage of 1250 mg/m^2 intravenously (over 30 minutes on days 1 and 8), carboplatin at an area under the curve of 5 (intravenous in 30 minutes on day 1) after gemcitabine. Routine anti-emetics were given according to institutional practice. No prophylactic growth factors were allowed.

Dose adjustments were made according to the guidelines described in Table 1. In the case of non-hematological toxicity grade 4, a dose reduction with 25% of both gemcitabine and carboplatin was performed.

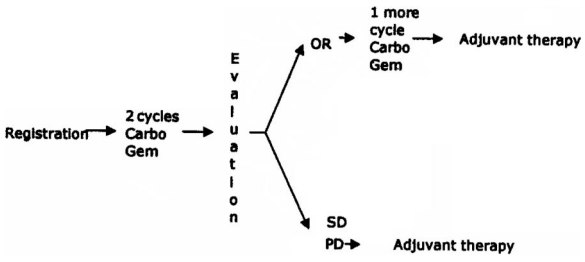

FIGURE 1. Treatment schedule

TABLE 1. Redosing schedule related to toxicity

Gemcitabine dose (mg/m^2)	WBC $\times 10^9$/L	ANC $\times 10^9$/L and/or	Platelets $\times 10^9$/L and/or
1250	>2	>1	>100
1000	1–2	0.5–1	50–100
0	<1	<0.5	<50

After two cycles, response evaluation was performed according to RECIST criteria. In case of a response, one more cycle was administered before the start of thoracic radiotherapy. In the case of stable disease or progressive disease, patients were immediately referred for radiotherapy. Radiotherapy was given with a radical intent. Dose was calculated taking into account lung toxicity (V20) and estimated esophagus toxicity. The interval between the start of the last chemotherapy and the start of radiotherapy had to be at least 4 weeks and less than 6 weeks. Toxicity was assessed weekly using the National Cancer Institute common toxicity criteria (NCI-CTC version 2). Radiation toxicity was scored according to RTOG criteria

Statistics:

The study was designed according to the two-step Simon design, with a response rate of interest after two cycles of chemotherapy of at least 70% with a type 1 error of 0.05 and a power of 80%; 37 patients had to be accrued to observe 26 responses. If less than 12 responses were seen in the first 24 patients, the study should have been discontinued. Response analysis was performed for eligible patients only. Toxicity analysis included all patients. Survival data were calculated using the Kaplan-Meier method.

RESULTS

Patient Characteristics

Between January 2002 and December 2004, 42 patients were enrolled (23 male, 19 female; mean age 61.3 years, range 42-78 years). All patients gave informed consent. Five patients were ineligible because of stage IV disease in four patients and stage IIIB disease with pleural effusion in one patient. Patient characteristics of the eligible patients are presented in Table 1.

Activity

A total of 102 chemotherapy courses were administered, with a median of three cycles per patient (range, one to four). Two patients with a partial response received four cycles instead of the planned three because of a delay in the start of radiotherapy because of logistical problems.

The overall clinical response rate in the 37 eligible patients was 51% (95% CI, 34%-68%) and for stage IIIA and IIIB disease 38% (9 of 16) and 61.9% (13 of 21), respectively, with no complete responses. No disease progression was observed.

TABLE 2. Patient Characteristics

Characteristic	No. of Patients (%)
Male/female	19/18 (51/49)
Age (yr)	61.8 (42–78)
PS 0	14 (38)
PS 1	21 (57)
PS 2	2 (5)
Stage IIIA	16 (43)
Stage IIIB	21 (57)

Values are *n*(%) or mean (range).

Toxicity and Dose Intensity

Five patients were excluded from the toxicity analysis, one because of erythropoietin administration and four because only data from cycle one were available. In the remaining 37 patients, grade 3 to 4 thrombocytopenia was seen in 13 patients (35.1%), with 12 (32.4%) grade 3 and 1 (2.6%) grade 4) (Table 2). Six patients required platelet transfusions, but no overt hemorrhages were observed. Grade 3 to 4 neutropenia was observed in 15 (40.5%) of patients: 13 (35.1%) grade 3 and 2 (5.2%) grade 4. No febrile neutropenia occurred. In one patient (2.6%), a grade 3 anemia was found, but erythrocyte transfusions were given in 10 patients (27%) (Table 3).

Except for dyspnea, which was found in five patients (13.2%), non-hematological toxicity was low.

The planned dose intensity was 208 mg/wk for carboplatin and 1542 mg/wk for gemcitabine. Relative dose intensity in the 37 patients equaled 99% for carboplatin and 91% for gemcitabine.

Radiation Therapy

Of the patients who received the planned treatment, 89% (33 of 37) underwent radiotherapeutic treatment. Four patients did not undergo radiotherapy. One patient died after chemotherapy before the start of radiation therapy because of myocardial infarction that was not related to chemotherapy. One patient had a marginal pulmonary function but was considered by a radiation oncologist to be fit for involved field radiotherapy. However, the patient's clinical condition deteriorated after chemotherapy, and he was subsequently judged to be unfit for radiotherapy. In two otherwise fit patients, the initial radiation fields were considered to be excessively large for radical radiotherapy, and we planned to irradiate the post-chemotherapy volume. A lack of response to chemotherapy led to the decision not to irradiate. These were the only two patients included in the study for who we planned to irradiate the post-chemotherapy volume. Mean dose was 42.5 Gy (range, 20-66 Gy). During and after radiotherapy, one patient developed grade 3 esophagitis. Radiation pneumonitis occurred in four patients (grade 1 in two patients and grade 3 in two patients).

TABLE 3. Hematological toxicity

	Grade 3	Grade 4
Anemia	1 (2.7)	0 (0)
Thrombocytopenia	12 (32.4)	1 (2.7)
Leukopenia	9 (24.3)	0 (0)
Neutropenia	13 (35.1)	2 (5.4)

Values are *n*(%). $n = 37$.

Follow-Up

Median survival of all 37 patients was 13 months. The Kaplan-Meier survival curve is presented in Figure 2. Currently 78% of patients have progressed. Median time to disease progression is 9.1 months.

DISCUSSION

In this phase II study designed to investigate the activity and safety of the gemcitabine-carboplatin combination as an induction regimen in sequential chemo-radiation for locally advanced NSCLC, an overall response rate of 51% was achieved. Table 4 summarizes the characteristics of the published data on the combination of gemcitabine and platinum in locally advanced NSCLC. Because consolidation treatment is different among the studies, no valid information on time to progression can be provided. For the cisplatin-based schemes, response rates after chemotherapy differ between 40% and 70%. In the earlier studies, gemcitabine-cisplatin was given in a 4-week schedule. In later studies, this was changed to a 3-week schedule. This was done because of toxicity (mostly hematological), because of which the gemcitabine on day 15 was often omitted. Only one other study with gemcitabine-carboplatin used as an induction regimen in locally advanced NSCLC has been published, with a response rate of 41 %.[9] Recent data were presented in the same patient group showing a response rate of 74%.[10] In the latter studies, the induction treatment was followed by concomitant treatment with chemoradiation.

In the absence of randomized data, no formal comparison can be made between cisplatin- and carboplatin-containing regimens for induction. It is unlikely that such a trial will ever be conducted because of the large sample size required

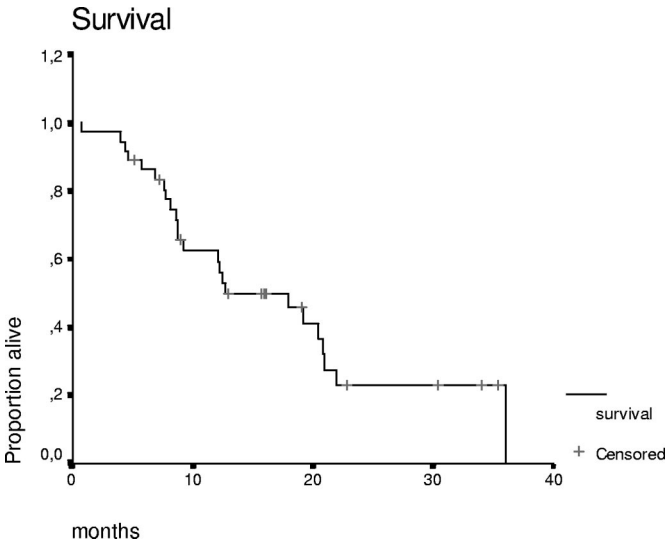

FIGURE 2. Survival curve for all 37 eligible patients.

TABLE 4 Articles about gemcitabine platinum in locally advanced NSCLC

Author	Phase	Induction scheme	q	*n*	Stage IIIa/IIIb (%)	Response rate (95% CI)
Van Zandwijk et al.[3]	II	Gemcitabine 1000 mg/m^2 d1,8,15 Cisplatin 100 mg/m^2 d2	4	47	100/0	70 (55-83)
Yang et al.[11]	II	Gemcitabine 1000 mg/m^2 d1,8,15 Cisplatin 90 mg/m^2 d15	4	52	50/50	64 (50-77)
Van Kooten et al.[12]	II	Gemcitabine 1250 mg/m^2 d1,8,15 Cisplatin 100 mg/m^2 d2	4	29	59/41	62 (45-79)
De Pas et al.[13]	II	Gemcitabine 1000 mg/m^2 d1,8,15 (1250 mg/m^2 d1,8) Cisplatin 100 d1 (80 mg/m^2 d1)	4 (3)	10 (40)	74/26	74 (60-85)
Santo et al.[14]	II	Gemcitabine 1250 mg/m^2 d1,8 Cisplatin 100 mg/m^2 d8	3	43	33/67	62 (NR)
Cappuzzo t al.[15]	II	Gemcitabine 1000 mg/m^2 d1,8 Cisplantin 70 mg/m^2 d2	3	129	44/56	62 (54-70)
Vokes et al.[1]	III	Gemcitabine 1250 mg/m^2 d1,8 Cisplatin 80 mg/m^2	3	62	67/33	40 (27-55)
Migliorino et al.[16]	II	Gemcitabine 1250 mg/m^2 d1,8 Cisplatin 70 mg/m^2 d2	3	69	67/33	57 (45-62)
Argiris et al.[8]	I/II	Gemcitabine 1000 mg/m^2 d1,8 Carboplatin AUC = 5	3	39	56/44	41 (26-56)
Current study	II	Gemcitabine 1250 mg/m^2 d1,8 Carboplatin AUC = 5	3	37	45/55	51 (34-68)

AUC, area under the curve.

to demonstrate a true difference. In advanced disease, such studies have been performed.[6,8] In neither of these studies was a significant difference in response rate between gemcitabine cisplatin or gemcitabine carboplatin found. In both studies, the response rate in the cisplatin arm was higher, but this did not reach statistical significance.

Toxicity was limited in the study. The known dose-limiting toxicity of the gemcitabine-carboplatin combination is hematologic.[6] Although thrombocytopenia grade 3 and 4 was present in 35% of cases, this was never associated with bleeding. Neutropenia grade 3 and 4 was present in 41% of patients, but no hospitalization because of febrile neutropenia was necessary. Anemia grade 3 was present in only one patient, but 10 patients received an erythrocyte transfusion, which may have influenced this number. Almost all transfusions were given after the completion of the second cycle. The high number of transfusions in relation to the objective toxicity numbers may be related to the fact that, in 12% of patients, grade 3 and 4 dyspnea was scored, which may have made physicians more prone to give blood transfusions. The toxicities are comparable to the numbers found in other studies.[6,9,11]

Survival of our patients was poor. We believe that this is related to the patient population included; most of our patients were stage IIIB. Patients with minimal N2 disease were included into other study protocols. The recent publication of Fournel et al.[3] also included a large population of patients with stage IIIB disease, and survival in the sequential arm was comparable to ours. Similarly, the recent phase III CALGB study 39801 evaluating two concurrent chemo-radiotherapy schedules reported median survivals of 11.4 months for concurrent chemo-radiotherapy, and 13.7 months for induction chemotherapy followed by the same concurrent chemo-radiotherapy scheme.[12]

In recent years, more and more data on the survival benefit of concurrent therapy have become available. At the time of the design of the study, these data were not published. It is therefore also likely that patients with good performance status were enrolled in this study. These patients will now preferably be treated with concurrent chemoradiotherapy. However, in a large group of patients, with poor performance status or with comorbid conditions, because of the toxicity of concurrent therapy, sequential therapy will remain standard of care. For these patients, the possibility of a lesser toxic chemotherapeutic agent is of importance, and, in these situations, carboplatin is preferred.

In conclusion, gemcitabine carboplatin is an active and safe chemotherapeutic regimen, especially for patients in whom cisplatin-based chemotherapy is contraindicated.

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